Studies on Proton Pump Inhibitors. III. Synthesis of 8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2-dihydroquinolines and Related Compounds

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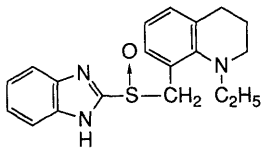
A series of 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2-dihydroquinolines (XIIIa—g) was synthesized and tested for ($H^+ + K^+$) adenosine triphosphatase (ATPase)-inhibitory and antisecretory activities. These compounds were synthesized by the oxidation of sulfides, which were obtained from the reaction of 8-chloromethyl-1,2-dihydroquinolines (XIa—c) and 2-mercaptobenzimidazoles in the presence of sodium hydride. The key intermediates, 8-hydroxymethyl-1,2-dihydroquinolines (IVa—c), were prepared by the reduction–alkylation of 8-acetoxymethyl- or 8-hydroxymethylquinolines with sodium cyanoborohydride–formic acid. Among XIIIa—g, the 1,4-dimethyl-1,2-dihydroquinoline derivative (XIIIa) was found to have the highest activity.

Keywords proton pump inhibitor; ($H^+ + K^+$)ATPase-inhibitory activity; 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2-dihydroquinoline; antisecretory activity; sodium cyanoborohydride

We have been searching for compounds having potent ($H^+ + K^+$) adenosine triphosphatase (ATPase)-inhibitory activity. In the previous paper,[1] we reported the synthesis and antiulcer activity of 8-[(2-benzimidazolyl)sulfinylmethyl]-1-ethyl-1,2,3,4-tetrahydroquinoline (OPC-22381, Chart 1) and related compounds. Some of them showed desirable antisecretory and antiulcer activities. As a continuation of our search for much more active compounds, we report here the synthesis and testing of 2-sulfinylbenzimidazoles having a 1,2-dihydroquinoline ring. 8-[(Benzimidazolyl)-sulfinylmethyl]-1,4-dimethyl-1,2-dihydroquinoline (XIIIa) was found to have the highest ($H^+ + K^+$)ATPase-inhibitory and antisecretory activities among the compounds synthesized.

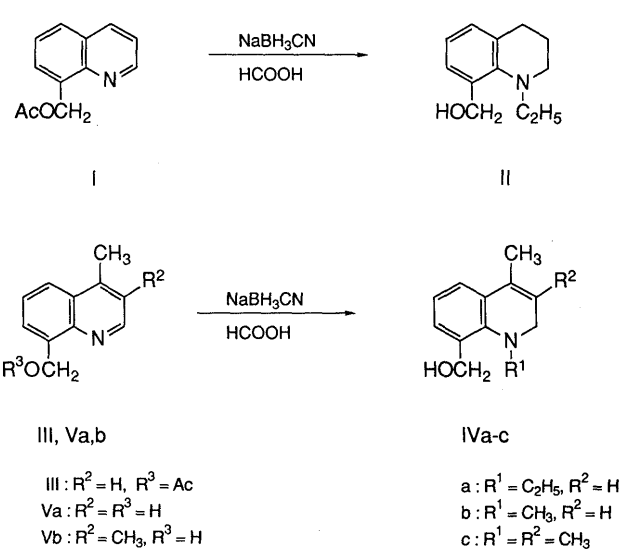


OPC-22381

Chart 1

Chemistry

In the course of an investigation aimed at synthesizing 1-substituted 8-hydroxymethyl-1,2,3,4-tetrahydroquinolines, we found that the treatment of 8-acetoxymethylquinoline (I) with sodium cyanoborohydride ($NaBH_3CN$)[2]–formic acid (HCO_2H) gave rise to the corresponding 1-ethyl-1,2,3,4-tetrahydroquinoline derivative (II) (Chart 2). We believe that the reaction I→II involves rearrangement of the acetyl group, followed by reduction of the resulting quinolinium compound to give II. This one-pot reduction–alkylation of quinoline is a very convenient method to prepare 1-ethyl-8-hydroxymethyl-1,2,3,4-tetrahydroquinoline. Likewise, the reaction of 8-acetoxymethyl-4-methylquinoline (III) with $NaBH_3CN$–HCO_2H gave 1-ethyl-8-hydroxymethyl-4-methyl-1,2-dihydroquinoline (IVa). Next, 8-hydroxymethyl-1-methyl-1,2-dihydroquinolines (IVb, c) were prepared from 8-hydroxymethylquinolines (Va, b) by reduction–alkylation with $NaBH_3CN$–HCO_2H (Chart 2). We found that the reaction of 4-methylquinolines unexpectedly gave 1,2-dihydroquinolines.



I, II

III, Va,b

III : R^2 = H, R^3 = Ac
Va : R^2 = R^3 = H
Vb : R^2 = CH_3, R^3 = H

IVa-c

a : R^1 = C_2H_5, R^2 = H
b : R^1 = CH_3, R^2 = H
c : R^1 = R^2 = CH_3

Chart 2

The preparation of the starting quinoline (Vb) is shown in Chart 3. 3,4,8-Trimethyl-2(1*H*)-quinolinone (VI)[3] was converted to the 2-chloroquinoline (VII) by treatment with phosphoryl chloride ($POCl_3$), followed by hydrogenation with palladium–charcoal to give 3,4,8-trimethylquinoline (VIII). Bromination of VIII with *N*-bromosuccinimide (NBS) in carbon tetrachloride (CCl_4) gave 8-bromomethyl-3,4-dimethylquinoline (IX), which was converted to the acetate (X) by treatment with sodium acetate in *N*,*N*-dimethylformamide (DMF), followed by hydrolysis with sodium hydroxide to give the alcohol (Vb).

Condensation of 2-mercaptobenzimidazoles with 8-chloromethyl-1,2-dihydroquinolines, which were synthesized by treatment of the 8-hydroxymethyl derivatives (IVa—c) with thionyl chloride, in the presence of sodium hydride afforded the corresponding sulfides (XIIa—g) (Table I). Various sulfinyl compounds (XIIIa—g) were prepared from sulfides (XIIa—g) by oxidation with *m*-chloroperbenzoic acid (m-CPBA) (Chart 4, Table II).

Biological Results

The ($H^+ + K^+$)ATPase-inhibitory and antisecretory

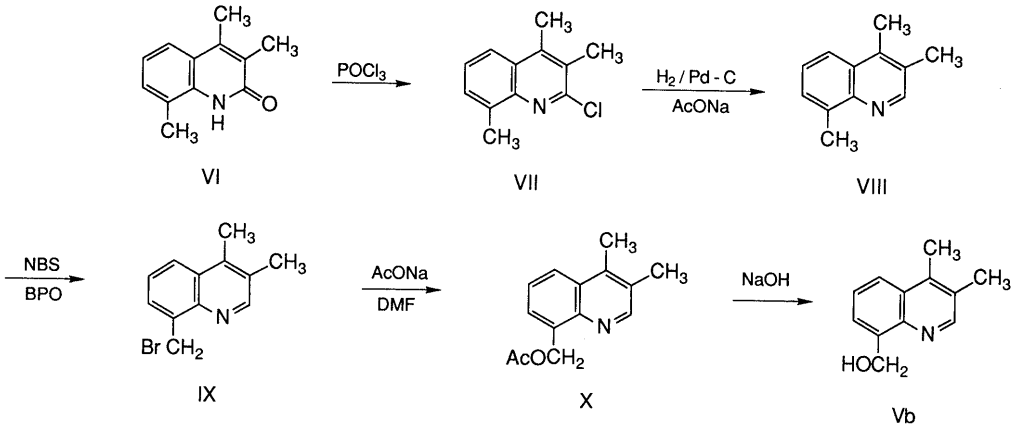


Chart 3

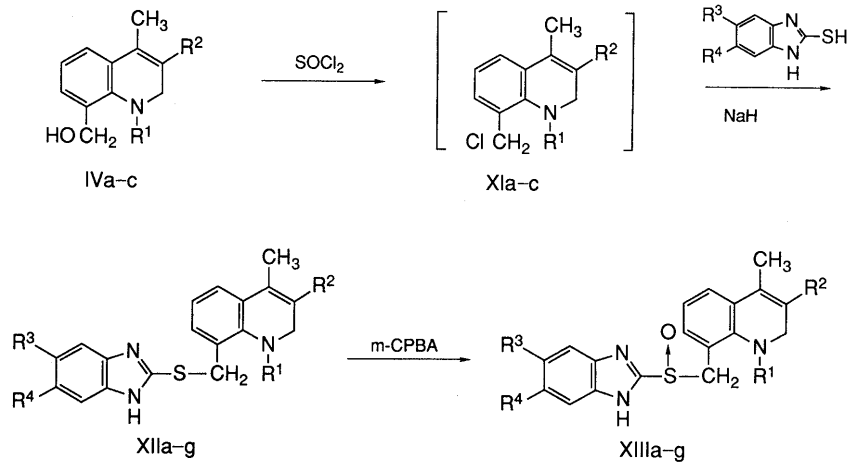
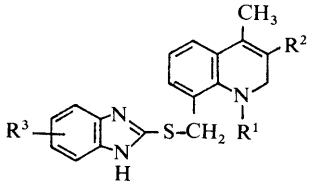


Chart 4

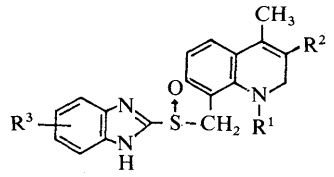
TABLE I. 8-[(2-Benzimidazolyl)thiomethyl]-1,2-dihydroquinolines



Compd. No.	R^1	R^2	R^3	Yield (%)	^{1}H-NMR ($CDCl_3$, J=Hz)
XIIa	CH_3	H	H	26	2.02 (3H, d, 1.5), 2.63 (3H, s), 3.50—3.80 (2H, m), 4.30 (2H, s), 5.50—5.70 (1H, m), 6.90—7.70 (7H, m), 12.87 (1H, br s)
XIIb	CH_3	H	5-CH_3	30	2.07 (3H, d, 1.5), 2.40 (3H, s), 2.72 (3H, s), 3.70—3.90 (2H, m), 4.30 (2H, s), 5.60—5.80 (1H, m), 6.80—7.50 (6H, m)
XIIc	CH_3	H	5-OCH_3	37	2.05 (3H, d, 1.5), 2.67 (3H, s), 3.60—3.90 (2H, m), 3.77 (3H, s), 4.30 (2H, s), 5.60—5.80 (1H, m), 6.70—7.50 (6H, m)
XIId	CH_3	H	5-F	32	2.06 (3H, d, 1.5), 2.69 (3H, s), 3.50—3.80 (2H, m), 3.83 (3H, s), 4.33 (2H, s), 5.50—5.70 (1H, m), 6.70—7.50 (5H, m), 12.60—13.00 (1H, br s)
XIIe	C_2H_5	H	6-OCH_3 H	27	1.30 (3H, t, 7), 2.09 (3H, d, 1.5), 3.00 (2H, q, 7), 3.81 (2H, s), 4.30 (2H, s), 5.70 (1H, s), 6.90—7.50 (7H, m), 13.04 (1H, br s)
XIIf	C_2H_5	H	5-F	40	1.22 (3H, t, 7), 2.06 (3H, d, 1.5), 2.95 (2H, q, 7), 3.60—3.80 (2H, m), 3.83 (3H, s), 4.32 (2H, s), 5.50—5.80 (1H, m), 6.90—7.50 (5H, m)
XIIg	CH_3	CH_3	6-OCH_3 H	30	1.88 (3H, s), 1.98 (3H, s), 2.60 (3H, s), 3.53 (2H, s), 4.29 (2H, s), 6.90—7.70 (7H, m)

activities of synthesized compounds are summarized in Table II. All compounds tested showed potent activity *in vitro*. These compounds, except XIIIf, inhibited *in vivo* histamine-induced gastric acid secretion in rats. The enzyme-inhibitory activity of 1,2-dihydroquinoline derivatives was similar to that of 1,2,3,4-tetrahydroquinoline

TABLE II. 8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2-dihydroquinolines



Compd. No.	R^1	R^2	R^3	H^+/K^+ ATPase IC_{50}, M[a]	Histamine-stimulated rat % inhibn. (at i.v. dose, mg/kg)[b]	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XIIIa	CH_3	H	H	6.4×10^{-7}	21.4 (3) 95.0 (10)	48	Pale brown powder (CH_2Cl_2–Et_2O)	159.5—160.5 (dec.)	$C_{19}H_{19}N_3OS$	67.63 (67.28)	5.68 5.71	12.45 12.21)
XIIIb	CH_3	H	5-CH_3	1.3×10^{-7}	11.5 (3) 90.8 (10)	41	Yellow granule (AcOEt–CH_2Cl_2)	132—133	$C_{20}H_{21}N_3OS$	68.35 (68.17	6.02 6.09	11.96 11.85)
XIIIc	CH_3	H	5-OCH_3	5.2×10^{-7}	70.7 (10)	34	Pale yellow needles (AcOEt)	148—149	$C_{20}H_{21}N_3O_2S$	65.37 (65.30	5.76 5.78	11.44 10.93)
XIIId	CH_3	H	5-F 6-OCH_3	2.7×10^{-6}	77.5 (10)	19	Pale yellow powder (CH_2Cl_2–Et_2O–hexane)	157—159 (dec.)	$C_{20}H_{20}FN_3O_2S$	62.32 (62.05	5.23 5.39	10.90 10.80)
XIIIe	C_2H_5	H	H	2.3×10^{-7}	29.5 (10) 100.0 (30)	12	White powder (Et_2O)	127—130 (dec.)	$C_{20}H_{21}N_3OS\cdot 1/2H_2O$	66.64 (66.34	6.15 5.91	11.66 11.42)
XIIIf	C_2H_5	H	5-F 6-OCH_3	2.5×10^{-6}	NE[c]	8	Pale yellow powder (Et_2O)	140—142 (dec.)	$C_{21}H_{22}FN_3O_2S\cdot 1/2H_2O$	61.75 (61.92	5.68 5.55	10.29 10.08)
XIIIg	CH_3	CH_3	H	5.5×10^{-7}	95.8 (10)	4	White powder (Et_2O)	148—149.5 (dec.)	$C_{20}H_{21}N_3OS$	68.35 (68.41	6.02 6.12	11.96 11.88)

a) Omeprazole, 2.0×10^{-6} M; OPC-22381, 1.9×10^{-7} M. *b*) Omeprazole, 78.6% (1 mg/kg); OPC-22381, 70.5% (3 mg/kg). *c*) NE = no effect.

derivatives, whereas their antisecretory activity was diminished with respect to 1,2,3,4-tetrahydroquinolines. Although the $(H^+ + K^+)$ATPase-inhibitory activities of the dihydroquinolines are more potent than that of omeprazole (2-[(3,5-dimethyl-4-methoxy-6-pyridyl)methylsulfinyl]-5-methoxybenzimidazole), their antisecretory activity was less than that of omeprazole. This suggests that these compounds may either be unable to permeate through the membrane or have poor stability. Among them, compound XIIIa was found to have the highest activity.

Experimental

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on Varian EM-390 and Bruker AC-200 NMR spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Varian MAT-312 instrument.

1-Ethyl-8-hydroxymethyl-1,2,3,4-tetrahydroquinoline (II) Formic acid (50 ml) was added dropwise under nitrogen to a stirred and ice-cooled suspension of 8-acetoxymethylquinoline (I, 5.7 g, 28 mmol) and $NaBH_3CN$ (8.8 g, 0.14 mol) in tetrahydrofuran (THF) (50 ml) and the reaction mixture was stirred at room temperature for 3 h. After removal of the solvent, the residue was poured into water and the solution was adjusted to pH 9 (NaOH) and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 4 : 1) to give II (2.9 g, 55%) as a yellow oil. NMR δ: 1.27 (3 H, t, J = 7.5 Hz), 1.66—2.00 (2H, m), 2.85 (2H, q, J = 7.5 Hz), 3.00—3.20 (2H, m), 4.00 (1H, br s), 4.75 (2H, s), 6.93 (3H, s). The product was identical with a sample prepared by the reported method.[1]

1-Ethyl-8-hydroxymethyl-4-methyl-1,2-dihydroquinoline (IVa) Compound IVa (3.2 g, 24%) was prepared by a similar procedure to that used for II with $NaBH_3CN$ (25.6 g), HCO_2H (160 ml) and 8-acetoxymethyl-4-methylquinoline (III, 14 g). NMR δ: 1.16 (3H, t, J = 7 Hz), 2.09 (3H, d, J = 1.5 Hz), 2.89 (2H, q, J = 7 Hz), 3.50—3.80 (2H, m), 4.81 (2H, s), 5.63 (1H, br s), 5.91 (1H, br s), 6.90—7.60 (3H, m). IR ν (neat): 3400, 2970, 2850, 1450, 1380, 1220, 760 cm^{-1}. MS *m/z* (%): 203 (M^+, 60), 202 (100), 176 (24), 172 (31), 157 (36), 156 (76), 144 (24), 142 (24).

8-Hydroxymethyl-1,4-dimethyl-1,2-dihydroquinoline (IVb) Compound IVb (0.9 g, 24%) was prepared by a similar procedure to that used for II with $NaBH_3CN$ (7.9 g), HCO_2H (50 ml) and 8-hydroxymethyl-4-methylquinoline (Va, 3.5 g). NMR δ: 2.08 (3 H, d, J = 1.5 Hz), 2.58 (3H, s), 3.50—3.70 (2H, m), 4.78 (2H, s), 5.50—5.70 (1H, m), 6.90—7.30 (3H, m). IR ν (neat): 3370, 2920, 2850, 1460, 1440, 1040, 1020, 810, 750 cm^{-1}. MS *m/z* (%): 188 (M^+, 43), 174 (18), 170 (14), 158 (25), 156 (11), 144 (14), 115 (12).

8-Hydroxymethyl-1,3,4-trimethyl-1,2-dihydroquinoline (IVc) Compound IVc (1.0 g, 25%) was prepared by a similar procedure to that used for II with $NaBH_3CN$ (7.9 g), HCO_2H (50 ml) and 3,4-dimethyl-8-hydroxymethylquinoline (Vb, 3.7 g). NMR δ: 1.89 (3H, s), 2.05 (3H, s), 2.57 (3H, s), 3.48 (2H, br s), 4.82 (2H, s), 6.11 (1H, br s), 6.90—7.30 (3H, m). IR ν (neat): 3400, 2950, 2870, 1470, 1460, 1030, 770 cm^{-1}. MS *m/z* (%): 203 (M^+, 50), 202 (100), 188 (66), 187 (23), 186 (22), 172 (22), 158 (25).

2-Chloro-3,4,8-trimethylquinoline (VII) 3,4,8-Trimethyl-2(1*H*)-quinolinone[3] (VI) (17.2 g, 92 mmol) was added to stirred and ice-cooled phosphoryl chloride (80 ml). The reaction mixture was heated at 90—110 °C for 2 h with stirring, then allowed to cool. The mixture was poured into ice-water. The precipitates were collected by filtration and recrystallized from EtOH to give VII (12.9 g, 68%) as a white powder, mp 91—93 °C. NMR δ: 2.53 (3H, s), 2.64 (3H, s), 2.75 (3H, s), 7.40—7.60 (2H, m), 7.80 (1H, d, J = 8 Hz). IR ν (KBr): 1580, 1500, 1390, 1320, 1170, 1010, 940, 760 cm^{-1}. *Anal.* Calcd for $C_{12}H_{12}ClN$: C, 70.07; H, 5.88; N, 6.81. Found: C, 69.67; H, 5.90; N, 6.72.

3,4,8-Trimethylquinoline (VIII) A mixture of VII (14.5 g, 70 mmol), AcONa (5.8 g) and 10% Pd–C (1.5 g) in AcOH (150 ml) was stirred at 60—70 °C under atmospheric pressure of hydrogen until the theoretical amount of hydrogen had been absorbed. The mixture was cooled to room temperature, the catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was poured into water and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from hexane to give VIII (10.4 g, 86%) as colorless prisms, mp 54.5—55.5 °C. NMR δ: 2.46 (3H, s), 2.59 (3H, s), 2.81 (3H, s), 7.30—8.00 (3H, m), 8.71 (1H, s). IR ν (KBr): 2960, 2930, 1510, 1390, 780, 770 cm^{-1}. *Anal.* Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.74; H, 7.70; N, 8.00.

8-Bromomethyl-3,4-dimethylquinoline (IX) A mixture of VIII (10.3 g, 60 mmol), NBS (10.7 g, 60 mmol) and benzoyl peroxide (BPO) (0.5 g) in CCl_4 (100 ml) was refluxed for 2 h. After removal of the precipitates by filtration, the filtrate was concentrated to give IX (14.5 g, 96%). The residue obtained was dissolved in EtOH containing HBr and concentrated to dryness. The product was recrystallized from EtOH to give IX HBr as brown needles, mp 270—272 °C (dec.). NMR δ: 2.43 (3H, s), 2.55 (3H, s), 5.20 (2H, s), 7.30—8.10 (3H, m), 8.75 (1H, s). IR ν (KBr): 3020, 2800, 2750, 1590, 1570, 1380, 1230, 820, 770 cm^{-1}. *Anal.* Calcd for $C_{12}H_{13}Br_2N$:

C, 43.54; H, 3.96; N, 4.23. Found: C, 43.40; H, 3.89; N, 4.19.

8-Acetoxymethyl-3,4-dimethylquinoline (X) A suspension of IX (15.8 g, 63 mmol) and AcONa (6.2 g, 76 mmol) in DMF (150 ml) was heated at 70—80 °C for 3 h with stirring and concentrated *in vacuo*. The residue was poured into water and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from hexane to give X (12.5 g, 86%) as a white powder. NMR δ: 2.13 (3H, s), 2.44 (3H, s), 2.68 (3H, s), 5.82 (2H, s), 7.30—8.10 (3H, m), 8.70 (1H, s). IR ν (KBr): 1730, 1380, 1260, 1250, 1230, 1030, 770 cm^{-1}. *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.19; H, 6.58; N, 6.04.

8-Hydroxymethyl-3,4-dimethylquinoline (Vb) A mixture of X (12.5 g, 55 mmol) and NaOH (3.3 g, 83 mmol) in MeOH (100 ml) was stirred for 1 h at room temperature. After removal of MeOH, the residue was poured into water and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 300 : 1) and recrystallized from AcOEt–hexane to give Vb (3.7 g, 36%) as colorless prisms, mp 80.5—82.5 °C. NMR δ: 2.49 (3H, s), 2.61 (3H, s), 5.17 (2H, s), 5.33 (1H, br s), 7.30—8.00 (3H, m). IR ν (KBr): 3420, 3150, 1510, 1390, 1060, 770 cm^{-1}. *Anal.* Calcd for $C_{12}H_{13}NO \cdot 1/2H_2O$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.43; H, 7.25; N, 6.99.

8-[(2-Benzimidazolyl)thiomethyl]-1,2-dihydroquinolines (XIIa—g): A Typical Procedure Thionyl chloride (0.6 g, 5 mmol) was added dropwise to a stirred and ice-cooled solution of IVa (0.9 g, 4.8 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was stirred at 0—10 °C for 0.5 h and then concentrated *in vacuo*. The residue was dissolved in DMF (30 ml) containing 2-mercaptobenzimidazole (0.7 g, 4.7 mmol) and 60% NaH (0.19 g, 4.8 mmol). The reaction mixture was stirred at the same temperature for 1 h. After removal of the solvent, the residue was poured into water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 200 : 1) to give XIIa (0.4 g, 26%) as an oil. IR ν (neat): 3050, 2950, 2870, 1440, 1410, 1270, 760, 740 cm^{-1}. MS *m/z* (%): 322 ($M^+ + 1$, 1), 173 (10), 172 (41), 171 (100), 157 (10), 150 (17). NMR data are given in Table I.

Compounds XIIb—g were obtained by a similar procedure to that described for XIIa; the yields and NMR data are listed in Table I.

8-[(2-Benzimidazolyl)sulfinylmethyl]-1,2-dihydroquinolines (XIIIa—g): A Typical Procedure A solution of 80% m-CPBA (0.27 g, 1.2 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred and cooled (−50—−40 °C) solution of XIIa (0.4 g, 1.2 mmol) in CH_2Cl_2 (30 ml) and the reaction mixture was stirred at the same temperature for 20 min. The solution was washed with Na_2CO_3 aqueous solution and dried over $MgSO_4$. After removal of the solvent, the residue was triturated in Et_2O. The precipitates were collected by filtration, and recrystallization from CH_2Cl_2–Et_2O gave XIIIa (0.2 g, 48%) as pale brown powder, mp 159.5—160.5 °C (dec.). NMR δ: 2.05 (3H, d, J = 1.5 Hz), 2.60 (3H, s), 3.40—3.60 (2H, m), 4.41 (1H, d, J = 13.5 Hz), 4.81 (1H, d, J = 13.5 Hz), 5.50—5.70 (1H, m), 6.80—7.80 (7H, m). IR ν (KBr): 3220, 1410, 1050, 740 cm^{-1}. The elemental analysis data are given in Table II.

Compounds XIIIb—g were obtained by a similar procedure to that described for XIIIa; the yields, melting points and elemental analysis data are listed in Table II.

Biological Methods The $(H^+ + K^+)$ATPase-inhibitory and gastric antisecretory activities were tested by the reported methods.[4]

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